Implementation of micelle enabled C(sp2)-C(sp3) cross-electrophile coupling in pharmaceutical synthesis

Bin Wu*[a], Ning Ye*[a], Kangming Zhao,[a] Min Shi,[a] Jiayu Liao,[a] Jing Zhang,[a] Wei Chen,[a] Xianzhong Li, [a] Yunfeng Han,[a] Margery Cortes-Clerget,[b] Morgan Louis Regnier,[b] Michael Parmentier,[b] Mathes Christan,[b] Florian Rampf,[b] Fabrice Gallou*[b]

[a]Chemical & Analytical Development, Suzhou Novartis Technical Development Co., Ltd, Changshu, Jiangsu 215537, China. Email: bin-3.wu@novartis.com; ning.ye@novartis.com;

[b]Chemical & Analytical Development, Novartis Pharma AG, 4056 Basel, Switzerland
Email:fabrice.gallou@novartis.com

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Materials and Methods

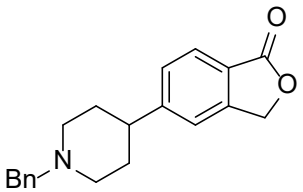
General. All chemicals, reagents, and solvents were purchased from commercial sources and were used without further purification unless otherwise noted. ^{1}H NMR data are reported relative to residual solvent signals and are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), and integration. The multiplicities are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at frequencies of 400 and 100 MHz respectively, using DMSO-d^6. Unless otherwise notice, the ^{1}H NMR experiments are performed at room temperature (298 K) and 16 times of scans by default; the ^{13}C NMR experiments are performed at room temperature (298 K) and 1024 times of scans by default. HRMS were obtained on Waters ACQUITY UPLC/Xevo G2 QTOF SYSTEM. UPLC analysis was performed on Agilent 1290 Infinity LC System.

Materials. Unless otherwise noted, commercial reagents were purchased from Aldrich, J&K Scientific Ltd., and other commercial suppliers and were used as received.

General procedure

Preparation of the catalyst/ligand solution: In reactor A was added $Ni(OAc)_2 \cdot 4H_2O$ (35 g, 5 mol%), 3,4,7,8-tetramethyl-1,10-phenanthroline (40 g, 6 mol%) and exchanged with N_2 atmosphere for three times. 2 wt% aqueous TPGS-750-M (4 kg) was added. The resulting mixture was stirred at 45 °C for 30 min to obtain a clear pink solution to be directly used in the following step.

General procedure for the reaction: In reactor B was added Me-THF (5.5 kg), 2 wt% aqueous TPGS-750-M (2 kg) and bubbling with N_2 for 60 mins. 1-benzyl-4-iodopiperidine-HCl salt **2a** (1.4 kg, 1.5 equiv.) was added followed by DIPEA (1.1 kg, 3 equiv.), and the resulting mixture was stirred at 45 °C for 3 h. Then 5-bromophthalide **1a** (0.6 kg, 1 equiv.), Cu_2O (6 g, 0.15 mol%) were added and the mixture was stirred at this temperature for 10 mins. The pre-mixed catalyst solution in reactor A was transferred to reactor B and zinc (0.46 kg, 2.5 equiv.) was added (Note: Thermal release was observed and adding zinc in portions is highly recommended). The resulting mixture was stirred at 45 °C for 16 h and the progress was monitored by HPLC analysis. Upon reaction completion, the zinc dust was removed by filtration via MCC (0.6 kg) and washed with additional Me-THF (2.6 kg). A two-layer solution was collected and layer separation to collect upper organic layer. The organic layer was concentrated (~6 kg distilled out) and to this reactor was added i-PrOH (2.8 kg). Continue to distill out 1.7 kg of organic solvent and raise the internal temperature to 70 °C to obtain a light brown clean solution. Water (10.5 kg) was added slowly during 2 h and stirred at this temperature for 1 h. The temperature was cooled to 20 °C over 3 h and stirred at this temperature for 10 h to obtain a suspension. Filtration to get the wet cake and drying under vacuum to obtain the desired product as a light brown solid.



5-(1-Benzylpiperidin-4-yl)isobenzofuran-1(3H)-one (3a): White solid; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.75 (d, J = 8.0 Hz, 1H), 7.54 (s, 1H), 7.47 (dd, J = 8.0, 1.4 Hz, 1H), 7.33 – 7.30 (m, 4H), 7.27 – 7.21 (m, 1H), 5.36 (s, 2H), 3.50 (s, 2H), 2.93 – 2.90 (m, 2H), 2.69 – 2.59 (m, 1H), 2.09 – 2.02 (m, 2H), 1.78 – 1.64 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6) δ 171.0, 153.8, 148.3, 139.0, 129.3, 128.6, 128.5, 127.3, 125.3, 123.5, 121.4, 70.2, 62.9, 53.9, 42.7, 33.3. HRMS (ESI) Calcd for $C_{20}H_{22}NO_2^+$ $[M + H]^+$ 308.1645, found 308.1640.

Table S1 Full ICP results for the two different batches of 1a (unit: ppm)

Sample	Ag	Al	As	B	Be	Bi	Ca	Cd	Co	Cr	Cu	Fe	K	Li	Mg	Mn	Na	Ni	P	Pb	Pd	Sb
Old	0.379	4.979	0.242	0.597	0.105	8.527	0.805	0.064	0.245	2.011	**947.845**	20.052	1.997	2.135	0.409	0.346	288.776	1.329	1044.080	21.099	0.048	3.820
New	0.116	5.420	0.079	0.307	0.043	0.325	14.387	0.021	0.112	3.278	**1.420**	41.290	1.508	0.491	3.948	0.705	1.330	0.755	2.765	41.756	0.059	2.961

P	Pb	Pd	Sb	Si	Sr	Ti	Zn	Rh	Ru	Sn
1044.080	21.099	0.048	3.820	5.711	0.065	0.452	41.810	0.470	0.007	1.453
2.765	41.756	0.059	2.961	4.160	0.211	0.257	1.263	0.116	0.250	2.452

Full Author names of reference *Cell. Chem. Biol.*, 2023, 30, 235.

Discovery and characterization of a selective IKZF2 glue degrader for cancer immunotherapy

Simone Bonazzi,[1,4,*] Eva d'Hennezel,[1,4,*] Rohan E.J. Beckwith,[1,4] Lei Xu,[1] Aleem Fazal,[1] Anna Magracheva,[1] Radha Ramesh,[1] Artiom Cernijenko,[1] Brandon Antonakos,[1] Hyo-eun C. Bhang,[1] Roxana García Caro,[1] Jennifer S. Cobb,[1] Elizabeth Ornelas,[2] Xiaolei Ma,[2] Charles A. Wartchow,[2] Matthew C. Clifton,[2] Ry R. Forseth,[3] Bethany Hughes Fortnam,[1] Hongbo Lu,[1] Alfredo Csibi,[1] Jennifer Tullai,[1] Seth Carbonneau,[1] Noel M. Thomsen,[1] Jay Larrow,[1] Barbara Chie-Leon,[2] Dominik Hainzl,[1] Yi Gu,[1] Darlene Lu,[1] Matthew J. Meyer,[1] Dylan Alexander,[1] Jacqueline Kinyamu-Akunda,[3] Catherine A. Sabatos-Peyton,[1] Natalie A. Dales,[1] Frédéric J. Zécri,[1] Rishi K. Jain,[1] Janine Shulok,[1] Y. Karen Wang,[1] Karin Briner,[1] Jeffery A. Porter,[1] John A. Tallarico,[1] Jeffrey A. Engelman,[1] Glenn Dranoff,[1] James E. Bradner,[1] Michael Visser,[1,4] and Jonathan M. Solomon[1,4,5,*]

[1]Novartis Institutes for Biomedical Research, Cambridge, MA, USA
[2]Novartis Institutes for Biomedical Research, Emeryville, CA, USA
[3]Novartis Institutes for Biomedical Research, East Hanover, NJ, USA
[4]These authors contributed equally
[5]Lead contact
*Correspondence: simone.bonazzi@novartis.com (S.B.), eva.dhennezel@novartis.com (E.d'H.), jonathan.solomon@novartis.com (J.M.S.)
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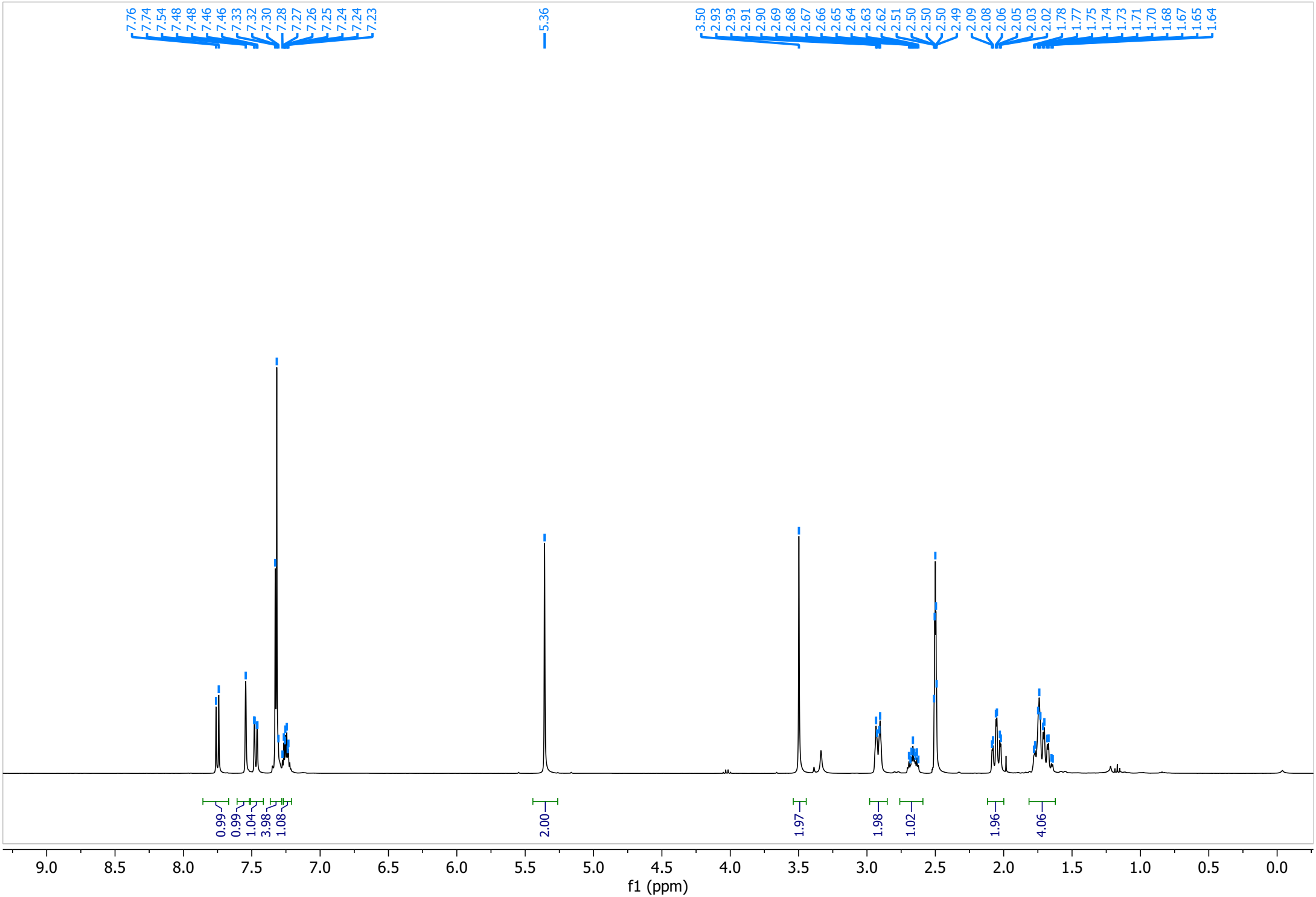
1H NMR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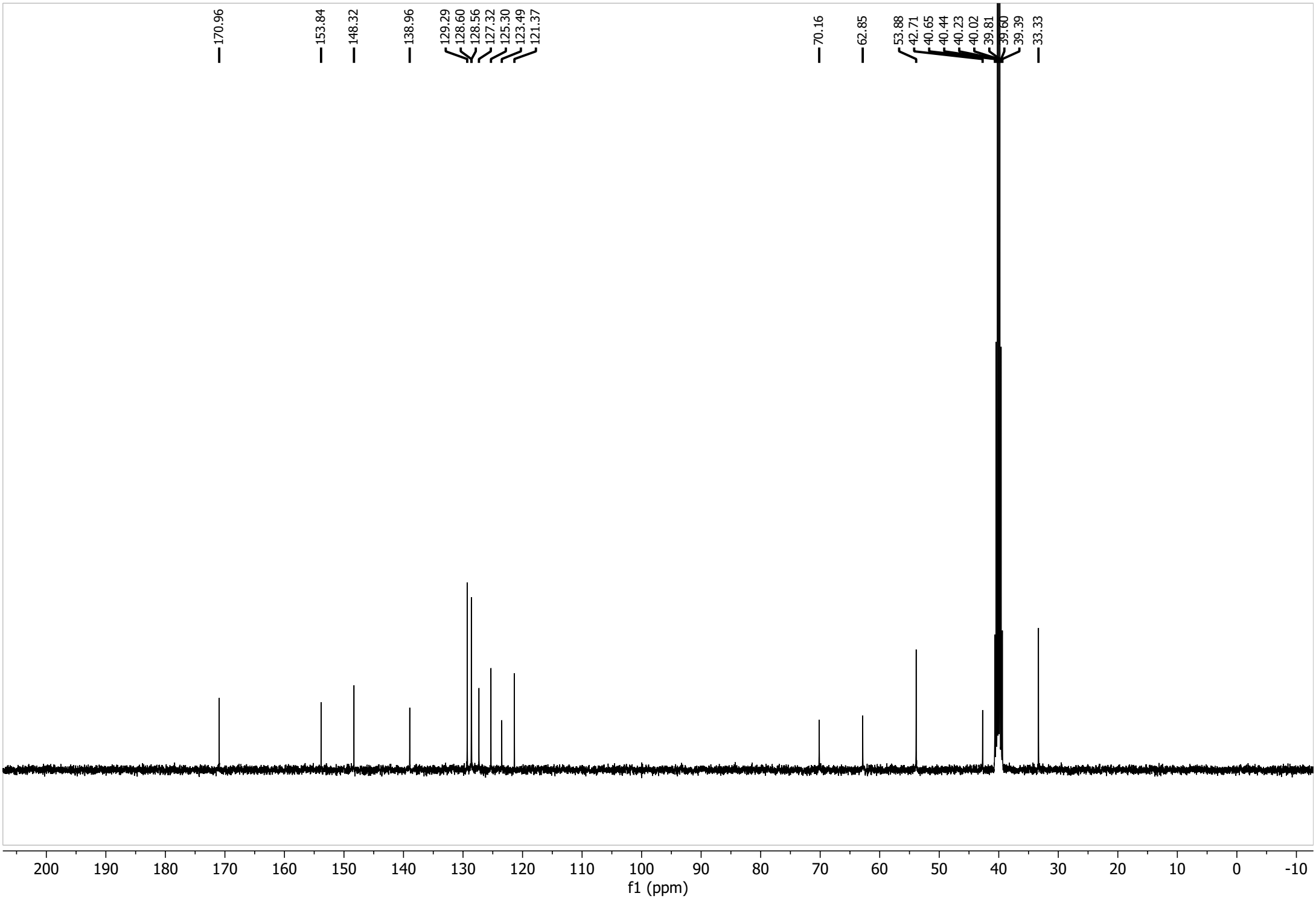
13C NMR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